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A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences

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Abstract

Objective—To investigate the prospective associations between early childhood lead exposure and subsequent risk of ADHD in childhood and its potential effect modifiers.

Study design—We analyzed data from 1479 mother-infant pairs (299 ADHD, 1180 neurotypical) in the Boston Birth Cohort (BBC). The child's first blood lead measurement and physician-diagnosed ADHD was obtained from electronic medical records. Graphic plots and multiple logistic regression were employed to examine dose-response association between lead exposure and ADHD and potential effect modifiers, adjusting for pertinent covariables.

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Results—We found that 8.9% of BBC children had elevated lead levels (5-10µg/dL) in early childhood, which was associated with a 66% increased risk of ADHD (OR=1.66, 95%CI:1.08, 2.56). Among boys, the association was significantly stronger (OR: 2.49, 95%CI:1.46, 4.26); in girls, the association was largely attenuated (p-value for sex-lead interaction: 0.017). The odds ratio of ADHD associated with elevated lead levels among boys was reduced by half if mothers had adequate high-density lipoprotein (HDL) levels compared with low HDL, or if mothers had low stress compared with high stress during pregnancy.

Conclusions—Elevated early childhood blood lead levels increased the risk of ADHD. Boys were more vulnerable than girls at a given lead level. This risk of ADHD in boys was reduced by half if the mother had adequate HDL levels or low stress. These findings shed new light on the sex difference in ADHD and point to opportunities for early risk assessment and primary prevention of ADHD.

Keywords

HDL; Stress; neurodevelopment disorder

Lead is a recognized environmental toxin.¹⁻⁵ Lead exposure has declined significantly over the past decades since the removal of lead from paints and gasoline and the adoption of other environmental safety measures.⁶ However, exposure to low lead levels continues to be widespread in the general U.S. population, particularly in urban low-income populations.⁷ To date, critical questions remain regarding the role of early life lead exposure in the development of ADHD.⁸⁻¹⁰ Existing studies used cross-sectional designs,^{2, 3, 5} and lead measurement occurred either simultaneous to or after the ADHD diagnosis, thus the temporal relationship between lead exposure and ADHD could not be established. Despite the well-observed higher likelihood of ADHD in males compared with females, few studies have investigated if lead affects boys and girls differently.² Additionally, most studies on ADHD examined lead exposure late in childhood (mean age of measurement ranging from 7 to 14 years).¹⁰ Lastly, prior studies did not consider potential modifiers of the lead-ADHD association, which is necessary both in terms of understanding the etiology of ADHD and informing intervention strategies.¹¹

In this study, we sought to examine the association between early childhood lead exposure and development of ADHD using a prospective birth cohort design. We were particularly interested in identifying early life factors that could modify lead-ADHD associations in a predominantly urban low-income minority population in the U.S. We hypothesized that there is a significant association between early childhood blood lead levels and the risk of developing ADHD. Motivated by findings from our previous work,¹² we further hypothesized that this association might be modified by prenatal factors, including child sex, maternal high-density lipoprotein (HDL) levels and degree of stress during pregnancy. The conceptual framework of these hypotheses is illustrated in Figure 1 (available at www.jpeds.com).

Methods

This study analyzed data from the Boston Birth Cohort (BBC), which recruited mother-infant pairs at birth from Boston Medical Center (BMC) since 1998, using a rolling enrollment. Details of the BBC recruitment have been published previously.^{13, 14} Eligible mothers were those who delivered a single live birth at Boston Medical Center (BMC). Pregnancies resulting from in vitro fertilization, multiple-gestation pregnancies, deliveries induced by maternal trauma, or newborns with substantial congenital disabilities were not eligible for enrollment. BBC mother-infant pairs who continued to receive pediatric primary care at BMC were enrolled in a postnatal follow-up study.^{13, 15, 16} The Institutional Review Board (IRB) of Boston University Medical Center and the IRB of Johns Hopkins Bloomberg School of Public Health approved the BBC study. Informed consent was obtained from each participant under the IRB approved protocol. There were 3098 mother-infant pairs enrolled in the postnatal follow-up study at BMC at the time of the study. Our study sample excluded participants who had missing data for lead measurements and key covariates. We further excluded those with lead measurement after ADHD diagnosis, incorrect lead measurement dates, lead measurement age older than 4 years, and a lead level higher than 10 µg/dL (to focus on the effects in the low lead exposure range). Because many neurodevelopmental disorders may have common risk factors, we excluded those with neurodevelopmental disorder diagnoses other than ADHD (Figure 2; available at www.jpeds.com). Our final analyses consisted of 1479 mother-infant pairs (299 children with ADHD and 1176 neurotypical children), who were enrolled at birth from 1998 to 2013 and followed-up prospectively until the end of 2016 (Figure 2).

After recruiting mothers within 24 to 72 hours after delivery, a standard questionnaire interview was used to collect data on maternal demographic characteristics, smoking status, and stress during pregnancy. Stress during pregnancy was defined according to the response to the following question: “How would you characterize the amount of stress in your life during pregnancy?” The possible responses to the question included: “not stressful,” “average stressful,” and “very stressful.” A medical abstraction form was used to review participants’ medical records and collect clinical-related data including parity, pregnancy-related complications, intrauterine infection, and birth outcomes such as gestational age and birthweight. Since 2003, electronic medical records (EMRs) were implemented for routine clinical data collection at BMC including both well-child and specialty medical visits. For each primary care visit, the EMRs contain the primary and secondary diagnoses from *the International Classification of Diseases, Ninth Revision* (ICD-9) (before October 1, 2015) and ICD-10 (after October 1, 2015). In this study, we extracted EMR data until the end of 2016.

Maternal plasma HDL levels and lead levels in red blood cells were measured using non-fasting blood samples obtained between 24 to 72 hours after delivery. The child postnatal blood lead levels (as part of routine pediatric screening) were obtained from the EMRs. The low detection limit of lead was 2 µg/dL; 659 children had blood lead levels below this threshold. The below threshold lead level was coded as 1 µg/dL when lead was analyzed as a continuous variable. For each child with repeated measurements of lead levels, the level measured at the earliest age was selected for analysis in this study.

In our study, the ADHD group was defined as having any of the following ICD-9 codes: [314.0, 314.00, 314.01, 314.1, 314.2, 314.8, and 314.9], or any of the following ICD-10 codes: [F90.0, F90.1, F90.2, F90.8, and F90.9] as documented in the child's EMRs. The neurotypical (NT) group was defined as not having any diagnosis of ASD, ADHD, conduct disorders, developmental delays, intellectual disabilities, failure to thrive, and/or congenital anomalies. Table I (available at www.jpeds.com) lists the ICD-9 and ICD-10 codes for these neurodevelopmental disorders diagnosis.

The characteristics of the study sample for the ADHD and the NT groups were compared using t-tests for continuous variables and χ^2 tests for categorical variables. Variables with a $P < .05$ were included in the subsequent multivariate logistic regression (MLR) analyses as covariates. The key predictor analyzed in this study was the child's lead level, which was natural log-transformed to approximate the normal distribution. Lead level was also analyzed as a binary (5 $\mu\text{g}/\text{dL}$ as the cutoff) and categorical variable (<2 $\mu\text{g}/\text{dL}$, 2-4 $\mu\text{g}/\text{dL}$, and 5-10 $\mu\text{g}/\text{dL}$) based on cut points used in previous studies and CDC guidelines.^{2, 8} Maternal HDL levels were analyzed as a binary variable cut at the median (60.7 mg/dL).¹² Maternal stress during pregnancy was converted from a 3-category variable (not stressful, average, very stressful) into a binary variable (not stressful vs. stressful) for analysis.¹⁷

We conducted multiple logistic regression (MLR) to examine the dose-response association between early childhood lead level and the risk of having ADHD, both categorically and continuously, adjusting for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight. Sex-stratified analyses and the joint effect of the child's sex with lead levels on the risk of ADHD diagnosis were tested using MLR, and adjusted for the same covariates except for child's sex. The interaction between child's sex and lead level on the risk of ADHD was then tested using MLR and adding the interaction term into the model while adjusting for the same covariates. We further tested the joint associations among maternal HDL level, maternal stress during pregnancy, and early childhood lead level with the risk of ADHD diagnosis both across and within the child's sex groups, adjusting for the same covariates except for child's sex. For the sensitivity analyses, we repeated the above analyses within three subsets: one analysis did not exclude the samples with other neurodevelopmental disorders; one analysis included the samples with early childhood lead levels measured at age 2 years; the third analysis further adjusted for maternal lead levels (treated as a binary variable cut at 5 $\mu\text{g}/\text{dL}$) measured right after delivery, using the samples that had measurements for both maternal and early childhood lead levels. We also performed cox proportional hazard models using child's age until the first ADHD diagnosis or administrative censor time at the end of 2016, adjusted for the same covariates as the MLR models. All analyses were performed using STATA version 14.0 software (Stata Corporation, College Station, TX, USA).

Results

Data from 1,479 mother-child pairs were analyzed. The median age of the children by our latest EMR extraction date (31 December 2016) was 9.6 years (inter-quartile range 7.4 to 12.5 years). Among them, 299 children (13.9% (before removing children with

neurodevelopmental disorders diagnoses other than ADHD) had a physician diagnosis of ADHD, and 131 children (8.9%) had lead levels of 5-10 µg/dL; 9.4% in boys and 8.3% in girls. The median age of the first diagnosis of ADHD was 6 years. The median age of the first lead measurement was 0.84 years (inter-quartile range 0.77 to 1.03 years). The comparison results of major characteristics between excluded and included samples indicate that the included sample had less exposure to multiple risk factors, such as less educational attainment, shorter gestational age, and lower birthweight (Table 2; available at www.jpeds.com). Table 3 presents the bivariate comparisons of maternal and child characteristics between the “ADHD” and “NT” groups. Mothers of children with any ADHD diagnosis were more likely to have less than a college degree, ever smoked before or during pregnancy, delivered by C-section, had high stress during pregnancy, and had low HDL levels compared with the NT group. Children with an ADHD diagnosis were more likely to be male, born prematurely, and have low birthweight, compared with the NT group.

Table 4 shows the results for both the crude and adjusted associations of early childhood lead levels with the risk of ADHD diagnosis. When lead levels were analyzed as three categories, compared with those with < 2 µg/dL lead levels, the adjusted OR for children with 2-4 µg/dL and 5-10 µg/dL lead levels was 1.08, 95% CI (0.81, 1.44) and 1.73, 95% CI (1.09, 2.73), respectively. The natural log-transformed linear trend of lead levels was significantly associated with an increased risk of ADHD diagnosis (adjusted OR=1.25, 95% CI (1.01, 1.56)). When lead was analyzed as a binary variable, children with 5-10 µg/dL lead levels had 66% increased odds of having any ADHD diagnosis as compared with children with <5 µg/dL lead levels (adjusted OR=1.66, 95% CI (1.08, 2.56)). A test of interaction between sex and lead level (binary) was statistically significant (p-value for interaction was 0.017), which was further explored as described below.

Figure 3 shows that the crude percentage of ADHD diagnosis was higher among boys compared with girls within each lead exposure level. Figure 4 (available at www.jpeds.com) is a Lowess plot showing a positive linear trend with the risk of ADHD diagnosis among boys, and the trend was flat among girls. Table 5 shows the adjusted associations between the child's lead levels and the risk of any ADHD diagnosis stratified by the child's sex and the joint effect of the child's lead levels and the child's sex on ADHD risk. When simultaneously considering child sex and lead levels, boys with 5-10 µg/dL lead levels had 7 folds increased odds of having any ADHD diagnosis (adjusted OR=7.48, 95% CI (4.29, 13.02)), compared with girls with < 5 µg/dL lead levels.

To further account for time to event, we plotted Kaplan-Meier (KM) survival curves stratified by child's sex and lead levels (Figure 5; available at www.jpeds.com) and performed cox proportional hazard models (Table 6; available at www.jpeds.com). Both analyses found similar associations of child sex and lead levels with ADHD diagnosis as those findings in Table 5 and Table 6.

Table 7 (available at www.jpeds.com) shows the results of the sensitivity analyses on the joint effects of early childhood lead exposure on ADHD diagnosis compared with the no ADHD group; and the findings were similar to those shown in Table 5. Table 8 (available at www.jpeds.com) shows the results of the sensitivity analyses on the joint effects of early

childhood lead exposure by restricting the analysis to children with lead measurements at age 2 years; and the findings were similar. Table 9 (available at www.jpeds.com) shows the results of the sensitivity analyses on the joint effects of early childhood lead exposure by further adjusting for maternal lead measurements right after delivery; and the findings were also similar. Figure 6 (available at www.jpeds.com) displays the plot of maternal lead levels vs. early childhood lead levels, which suggests no clear correlation between the two lead measures.

Table 10 (available at www.jpeds.com) shows the joint association of child's sex, maternal HDL level, maternal stress during pregnancy, and early childhood lead measurement with the risk of ADHD diagnosis. Compared with girls with low lead levels ($< 5 \mu\text{g/dL}$) and adequate maternal HDL levels ($> 60.7 \text{ mg/dL}$), boys with high lead levels and lower maternal HDL levels had 10 folds increased odds of having any ADHD diagnosis (OR=10.03, 95% CI [4.38, 22.97]). This increased risk was reduced by more than half if the mother had adequate maternal HDL levels (OR=4.77, 95% CI (1.76, 12.90)).

Similarly, boys with high lead levels and high maternal stress during pregnancy had almost 15 folds increased odds of having any ADHD diagnosis, compared with girls with low lead levels and low maternal stress (OR=14.94, 95% CI [6.88, 32.41]). This increased risk was reduced by more than half if the mother had low maternal stress during pregnancy (OR=6.10, 95% CI [2.18, 17.08]). Figure 7 (available at www.jpeds.com) shows the percentage of ADHD diagnosis by maternal HDL level, maternal stress during pregnancy, and early childhood lead measurement groups among boys. The within sex group comparison together with the findings shown in Figure 7 also indicate that the risk of ADHD diagnosis was lower for those born to mothers with adequate maternal HDL and low maternal stress during pregnancy given the same level of lead exposures for boys.

Table 11 (available at www.jpeds.com) and Table 12 (available at www.jpeds.com) show the additional sensitivity analyses to examine the independent and joint effect of gestational age and birthweight with early childhood lead exposure on ADHD. There was no indication of interaction between early childhood lead exposures and gestational age on ADHD, and the same is true for birthweight.

Discussion

This study demonstrates that moderately elevated levels (5-10 $\mu\text{g/dL}$) in early childhood are associated with an increased risk of ADHD in a U.S. predominantly urban, low-income minority birth cohort. Our findings are consistent with previous research regarding the effects of lead exposure on the risk of ADHD, although existing data were mostly cross-sectional in design.¹⁰ Our study has contributed new information to the field.

We revealed a significant sex difference in the association between lead exposure and ADHD. When we stratified the MLR analysis by sex, we found no significant association between elevated lead levels (5-10 $\mu\text{g/dL}$) and ADHD among girls, but a strong association with ADHD among boys, a finding not explained by a sex difference in lead exposure. Moreover, a small prospective study (n=195) also found similar boy-specific lead effects,

which revealed that both prenatal and childhood average lead levels (<78 months) were associated with attention factor of neuropsychological measures only within boys.²⁰ Taken together, the findings from previous studies and ours suggest that boys are more vulnerable than girls to the adverse effects of early life low level lead exposures.

In the context of early childhood lead exposure and ADHD in boys, we identified several potential protective factors that may attenuate the lead-ADHD association. We found that high maternal HDL levels and low maternal stress during pregnancy could partially counteract the increased odds of ADHD associated with early life lead exposure in boys. Except for the subgroups with sample sizes that were too small, our findings showed that high maternal HDL levels and low maternal stress during pregnancy could reduce the odds of ADHD by more than half compared with their counterparts. Conversely, boys born to mothers with low HDL and high stress during pregnancy were more vulnerable to the adverse effects of lead exposure on the risk of ADHD, given their level of lead exposure.

Within a subset of samples with both early childhood and maternal blood lead levels measured at delivery, we further explored if the association we identified could be altered if we further adjusted for maternal lead levels. We found that the sex-specific relationship between the early childhood lead level and the risk of ADHD remained even after adjusting for maternal lead levels. Furthermore, we found no significant correlation between maternal lead levels and early childhood lead levels. This finding is consistent with the correlation results reported in a previous study, which measured the lead levels of nearly 100 mother-child pairs from Montevideo, Uruguay.²¹

Although lead exposure in children has declined in the U.S. since the ban of leaded gasoline,⁹ lead exposure has remained a significant risk factor for certain segments of children for two major reasons. First, accumulating evidence has revealed that even low-level lead exposures still have adverse effects on neurodevelopment. As a result, the identified blood lead level of concern for the fetus or young child has been revised many times from 40 µg/dL to the current CDC guidelines which specify that there is no safe level of exposure.^{6, 9, 22–24} Indeed, more recent research lends even further support for the CDC guidelines that there is no threshold for the adverse health effects of lead exposure.^{8, 9}

Second, although any exposure is considered unsafe, there still are profound disparities in who is more exposed to lead in the U.S. A study conducted in South Carolina showed that the soil lead concentration was much higher in urban areas because of more potential lead sources based there, such as road networks and industries.²⁵ Related to this, low-income and racial/ethnic minority individuals, including children aged younger than 6 years, have a much higher risk of lead exposure because they are the ones who tend to live in these urban areas and in neighborhoods that are closer to these lead sources.²⁵ Additionally, children are more biologically susceptible to the toxic effects of lead compared with adults due to their much higher gastrointestinal bioaccessibility to lead.²⁶ In the BBC, about 9% of children had blood lead levels above 5 µg/dL. Consistently, many other studies have also found that low-income minority populations are more likely to live in highly lead-contaminated areas and have higher median blood lead concentrations, particularly among children.^{25, 27–29} Thirdly, our data suggest that urban low-income populations may be more vulnerable to lead

toxicity due to other risk factors including maternal dyslipidemia and high stress, as we demonstrated in this study. As such, lead remains a significant public health concern, especially for poor pregnant mothers and their children living in lead-contaminated areas.

The exact neurotoxicological pathways by which lead exposure affects ADHD risk remain unclear. Current biological studies suggest that lead disrupts the hippocampal region of the brain through interaction with the N-methyl-D-aspartate receptor both synaptically and extra-synaptically.³⁰ The lead-induced damage in the developing brain preferentially occurs in the prefrontal cortex (PFC), hippocampus, and cerebellum,^{31–33} and not surprisingly the brains of individuals with ADHD also show a reduction in the volume and activity of the PFC and cerebellum.³⁴ The neurotoxicity induced by lead depends on both age³⁵ and lead exposure level.³⁶ Compared with adults, children not only absorb more lead, but they do so directly into the brain due to a higher potential intake from the environment and an underdeveloped blood-brain barrier.^{37, 38} Moreover, the fetus is also at a high risk of lead exposure via transplacental transfer during pregnancy, which is a particularly sensitive period for fetal central nervous system development.^{39, 40}

The striking sex difference in ADHD is well-observed but poorly understood. An animal study showed that lead toxicity behaves differently in males and females.⁴¹ After treating with lead acetate, female rabbits showed an earlier and higher increase in Zn protoporphyrin (a screening marker for lead poisoning⁴²) than males.⁴¹ However, to date, no study has explained the biological mechanism behind male dominance in ADHD and sex differences in lead neurotoxicity in humans. Some have postulated that the sex difference in the lead-ADHD association might be explained by the sex difference in lead metabolism.^{43, 44} Over 90% of lead is stored in bone with an average of a 10 year half-life.⁴³ A study on occupational lead exposure showed that the rate of bone lead release for women is slower than it is for men.⁴⁴ Moreover, a study of Swedish twins showed that the genetic factors related to lead uptake and storage explain nearly 60% of the blood lead levels among nonsmoking women. In contrast, nonsmoking men's blood lead levels mainly reflect environmental exposures. One study identified three polymorphic genes that influence lead accumulation and toxicokinetics.⁴⁵ These genes are responsible for encoding enzyme delta-aminolevulinic acid dehydratase (ALAD), the vitamin D receptor (VDR), and the human hemochromatosis (HFE) protein.⁴⁵ It is possible that the weak association between blood lead levels and risk of ADHD among girls might be due to a sex difference in the frequency and expression of these genes.⁴⁶

Our study had several limitations. First, the early childhood blood lead measurements obtained during routine pediatric screening could not precisely assess the very lowest lead exposures due to a detection limit of 2 µg/dL. As a result, we could not examine the dose-response relationship between lead levels below 2 µg/dL and ADHD.² Second, the EMR data used in our study (2003–2016) spanned the transition of the diagnostic and statistical manual (DSM) from the DSM-IV-TR to the DSM-V edition.⁴⁷ However, this transition did not affect our ADHD determination⁴⁸ in children, because the main changes from DSM-IV-TR to DSM-V were more relevant to the adult diagnostic criteria. Third, missing information on lead levels and major covariates can cause selection bias if the missing is not at random. However, we compared children with and without lead measurements and did not find a

systematic difference among major covariates. Lastly, although we adjusted for multiple major risk factors identified in previous studies, data related to multiple family-related factors such as poor parenting,^{49, 50} maltreatment,⁵¹ conflict/parent-child hostility,⁵² and severe early deprivation^{53, 54} were not available in BBC. Thus, we could not wholly eliminate potential residual confounding in this study. However, those factors are less likely to share the same biological mechanism in their effect on neurodevelopment. Thus, we do not anticipate they had a significant impact on the association between early childhood lead and risk of ADHD even if it was possible to adjust for those factors.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
BBC	Boston Birth Cohort
HDL	high-density lipoprotein

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Figure 1.

online. Conceptual framework for the prospective association of early childhood lead exposure and development of ADHD in childhood from a life course perspective.

Figure 2. online. Flowchart of the Boston Birth Cohort study participants included in the analysis.

Figure 3.

The percentage of ADHD diagnosis in the BBC children, stratified by child's sex and early childhood lead measurement groups.

Figure 4. online. The crude relationship between early childhood lead exposure and ADHD diagnosis by child's sex.

Figure 5.
online. Kaplan-Meier (KM) survival curves stratified by child's sex and lead levels.

Figure 6.
online. The crude relationship between maternal lead levels and early childhood lead levels.

Figure 7. online. The percentage of ADHD diagnosis in subgroups defined by early childhood lead measurement and maternal HDL level (top), as well as maternal stress during pregnancy (bottom) among boys.

Table 1

online. List of ICD-9 and ICD-10 codes for the diagnosis of each neurodevelopmental disorder.

Neurodevelopmental disorder	ICD-9 codes	ICD-10 codes
ASD	299.0, 299.00, 299.01, 299.8, 299.80, 299.81, 299.9, 299.90, 299.91	F84.0, F84.8, F84.9
ADHD	314.0, 314.00, 314.01, 314.1, 314.2, 314.8, 314.9	F90, F90.0, F90.1, F90.2, F90.8, F90.9
Disturbance of conduct	312.0-312.9	F91, F91.0, F91.2, F91.3, F91.8, F91.9
Delays in development	315.0-315.9	F81.0, R48.0, F81.81, F81.2, F81.89, F80.1, F80.2, H93.25, F80.4, F80.81, F80.0, F80.82, F80.89, F82, F88, F81.9, F89
Intellectual disabilities	317-317	F70, F71, F72, F73, F78, F79
Failure to thrive	783.4, 783.40, 783.41, 783.42, 783.43	R62.50, R62.51, R62.0, R62.52
Congenital anomalies	740-759.9	Q00-Q99

Table 2

online. Maternal and child characteristics for participants excluded and included in the analysis.

Variable	Total	Excluded	Included	P-value ^a
Total	3098 (100)	1619 (52.26)	1479 (47.74)	
Maternal Age (years, <i>n</i> (%))				0.106
<20	288 (9.30)	138 (8.52)	150 (10.14)	
20-34	2246 (72.50)	1165 (71.96)	1081 (73.09)	
>=35	556 (17.95)	308 (19.02)	248 (16.77)	
Education level, <i>n</i> (%)				<0.001
Below college degree	2642 (85.28)	1401 (86.53)	1241 (83.91)	
College degree or above	420 (13.56)	182 (11.24)	238 (16.09)	
Maternal race, <i>n</i> (%)				<0.001
Black	1965 (63.43)	940 (58.06)	1025 (69.30)	
White	227 (7.33)	115 (7.10)	112 (7.57)	
Hispanic	682 (22.01)	448 (27.67)	234 (15.82)	
Others	209 (6.75)	101 (6.24)	108 (7.30)	
Smoking during pregnancy, <i>n</i> (%)				0.412
Never	2496 (80.57)	1277 (78.88)	1219 (82.42)	
Quitter	238 (7.68)	128 (7.91)	110 (7.44)	
Continuous	330 (10.65)	180 (11.12)	150 (10.14)	
Child's sex, <i>n</i> (%)				0.008
Female	1529 (49.35)	762 (47.07)	767 (51.86)	
Male	1567 (50.58)	855 (52.81)	712 (48.14)	
Delivery type, <i>n</i> (%)				0.057
C-section	1116 (36.02)	606 (37.43)	510 (34.48)	
Vaginal	1967 (63.49)	998 (61.64)	969 (65.52)	
Gestational age, week				<0.001
Mean $\pm$ SD	37.6 $\pm$ 3.5	37.1 $\pm$ 3.9	38.2 $\pm$ 3.0	
Birthweight, g				<0.001
Mean $\pm$ SD	2898.3 $\pm$ 819.7	2794.7 $\pm$ 881.7	3011.6 $\pm$ 729.5	

Note:

^aThe p-values were obtained from chi-square test or t-test between children included and excluded in the main analysis.

Table 3

Maternal and child characteristics for children with any ADHD diagnosis (ADHD) and neurotypical (NT) children.

Variable	Total	NT	ADHD	P-value ^a
Total	1,479 (100)	1,180 (79.78)	299 (20.22)	
Maternal Age (years, <i>n</i> (%))				0.094
<20	150 (10.14)	110 (9.32)	40 (13.38)	
20-34	1,081 (73.09)	874 (74.07)	207 (69.23)	
≥35	248 (16.77)	196 (16.61)	52 (17.39)	
Education level, <i>n</i> (%)				0.033
Below college degree	1,241 (83.91)	978 (82.88)	263 (87.96)	
College degree or above	238 (16.09)	202 (17.12)	36 (12.04)	
Maternal race, <i>n</i> (%)				0.137
Black	1025 (69.30)	811 (68.73)	214 (71.57)	
White	112 (7.57)	96 (8.14)	16 (5.35)	
Hispanic	234 (15.82)	181 (15.34)	53 (17.73)	
Others	108 (7.30)	92 (7.80)	16 (5.35)	
Parity, <i>n</i> (%)				0.715
Nulliparous	649 (43.88)	515 (43.64)	134 (44.82)	
Multiparous	830 (56.12)	665 (56.36)	165 (55.18)	
Smoking during pregnancy, <i>n</i> (%)				<0.001
Never	1219 (82.42)	995 (84.32)	224 (74.92)	
Quitter	110 (7.44)	71 (6.02)	39 (13.04)	
Continuous	150 (10.14)	114 (9.66)	36 (12.04)	
Intrauterine infection, <i>n</i> (%)				0.073
No	1283 (86.75)	1033 (87.54)	250 (83.61)	
Yes	196 (13.25)	147 (12.46)	49 (16.39)	
Child's sex, <i>n</i> (%)				<0.001
Female	767 (51.86)	681 (57.71)	86 (28.76)	
Male	712 (48.14)	499 (42.29)	213 (71.24)	
Delivery type, <i>n</i> (%)				0.021
C-section	510 (34.48)	390 (33.05)	120 (40.13)	
Vaginal	969 (65.52)	790 (66.95)	179 (59.87)	
Season of child's birth, <i>n</i> (%)				0.077
Jan to March	346 (23.39)	282 (23.90)	64 (21.40)	
April to June	355 (24.00)	282 (23.90)	73 (24.41)	
July to September	400 (27.05)	303 (25.68)	97 (32.44)	
October to December	378 (25.56)	313 (26.53)	65 (21.74)	
Preterm birth (<37 weeks, <i>n</i> (%))				<0.001
No	1,156 (78.16)	954 (80.85)	202 (67.56)	
Yes	323 (21.84)	226 (19.15)	97 (32.44)	
Low birthweight (<2,500 g, <i>n</i> (%))				<0.001

Variable	Total	NT	ADHD	P-value ^a
No	1,164 (78.70)	963 (81.61)	201 (67.22)	
Yes	315 (21.30)	217 (18.39)	98 (32.78)	
Stress during pregnancy, <i>n</i> (%)				<0.001
Not stressful	562 (38.00)	475 (40.25)	87 (29.10)	
Stressful	909 (61.46)	700 (59.32)	209 (69.90)	
Gestational age, week				<0.001
Mean $\pm$ SD	38.2 $\pm$ 3.0	38.5 $\pm$ 2.5	37.1 $\pm$ 4.2	
Birthweight, g				<0.001
Mean $\pm$ SD	3011.6 $\pm$ 729.5	3069.9 $\pm$ 665.4	2781.6 $\pm$ 906.3	
Early Childhood lead, μ g/dL				0.009
Mean $\pm$ SD	2.2 $\pm$ 1.6	2.1 $\pm$ 1.5	2.4 $\pm$ 1.9	
Maternal HDL, mg/dL				0.001
Median (25 th -75 th quantile)	60.7 (50.3-72.3)	61.5 (51.0-73.9)	57.4 (49.3-67.5)	

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis;

^aThe p-values were obtained from chi-square tests for categorical variables or t-tests for continuous variables, between children with ADHD and the NT controls.

Table 4

The association of early childhood lead levels with the risk of ADHD diagnosis.

Variables	ADHD, n (%)	NT, n (%)	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Lead log linear trend	299 (20.22)	1180 (79.78)	1.24	(1.01, 1.53)	0.037	1.25	(1.01, 1.56)	0.045
Lead: three categories								
<2 µg/dL	125 (18.97)	534 (81.03)	1.00			1.00		
2-4 µg/dL	136 (19.74)	553 (80.26)	1.05	(0.80, 1.38)	0.720	1.08	(0.81, 1.44)	0.622
5-10 µg/dL	38 (29.01)	93 (70.99)	1.75	(1.14, 2.67)	0.010	1.73	(1.09, 2.73)	0.019
Lead: binary								
<5 µg/dL	261 (19.36)	1087 (80.64)	1.00			1.00		
5-10 µg/dL	38 (29.01)	93 (70.99)	1.70	(1.14, 2.54)	0.009	1.66	(1.08, 2.56)	0.020

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

Table 5

The joint association of child's sex and early childhood lead levels with the risk of ADHD diagnosis.

Sex	Lead Level	ADHD, n (%)	NT, n (%)	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Female		86 (11.21)	681 (88.79)	1.00			1.00		
Male		213 (29.92)	499 (70.08)	3.38	(2.57, 4.45)	<0.001	3.42	(2.57, 4.55)	<0.001
Test for sex-based lead (binary) interaction									
Lead effects within child's sex									
Female	<5 µg/dL	80 (11.38)	623 (88.62)	1.00			1.00		
	5-10 µg/dL	6 (9.38)	58 (90.63)	0.81	(0.34, 1.93)	0.627	0.68	(0.27, 1.69)	0.401
Male	<5 µg/dL	181 (28.06)	464 (71.94)	1.00			1.00		
	5-10 µg/dL	32 (47.76)	35 (52.24)	2.34	(1.41, 3.90)	0.001	2.49	(1.46, 4.26)	0.001
Joint effects of child's sex and lead									
Female	<5 µg/dL	80 (11.38)	623 (88.62)	1.00			1.00		
	5-10 µg/dL	6 (9.38)	58 (90.63)	0.81	(0.34, 1.93)	0.627	0.69	(0.28, 1.71)	0.426
Male	<5 µg/dL	181 (28.06)	464 (71.94)	3.04	(2.27, 4.06)	<0.001	3.02	(2.24, 4.06)	<0.001
	5-10 µg/dL	32 (47.76)	35 (52.24)	7.12	(4.18, 12.13)	<0.001	7.48	(4.29, 13.02)	<0.001

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

online. The joint association of child's sex and early childhood lead levels with the risk of ADHD diagnosis using cox proportional hazard model.

Table 6

Child's sex	Lead Level	ADHD, No. (%)	NT, No. (%)	Hazard Ratio	95% CI	P-Value
	<5 µg/dL	261 (19.36)	1087 (80.64)	1.00		
	5-10 µg/dL	38 (29.01)	93 (70.99)	1.28	(0.92, 1.80)	0.134
Lead's effects within child's sex group						
Female	<5 µg/dL	80 (11.38)	623 (88.62)	1.00		
	5-10 µg/dL	6 (9.38)	58 (90.62)	0.65	(0.31, 1.36)	0.255
Male	<5 µg/dL	181 (28.06)	464 (71.94)	1.00		
	5-10 µg/dL	32 (47.76)	35 (52.24)	1.60	(1.10, 2.32)	0.014
Joint effects of child's sex and lead						
Female	<5 µg/dL	80 (11.38)	623 (88.62)	1.00		
	5-10 µg/dL	6 (9.38)	58 (90.62)	0.71	(0.34, 1.47)	0.362
Male	<5 µg/dL	181 (28.06)	464 (71.94)	2.48	(1.91, 3.22)	<0.001
	5-10 µg/dL	32 (47.76)	35 (52.24)	3.94	(2.62, 5.94)	<0.001

Note: NT is defined as without any mental disorder diagnosis; ADHD is defined as any ADHD diagnosis; the cox proportional hazard model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

Table 7

online. The joint association of child's sex and early childhood lead levels with the risk of ADHD diagnosis comparing to no ADHD group.

Sex	Lead Level	ADHD, n (%)	No ADHD, n (%)	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Female		86 (8.05)	982 (91.95)	1.00			1.00		
Male		213 (19.54)	877 (80.46)	2.77	(2.12, 3.62)	<0.001	2.84	(2.16, 3.72)	<0.001
Test for sex-based lead (binary) interaction									
Lead effects within child's sex									
Female	<5 µg/dL	80 (8.06)	912 (91.94)	1.00			1.00		
	5-10 µg/dL	6 (7.89)	70 (92.11)	0.98	(0.42, 2.32)	0.958	0.82	(0.34, 2.01)	0.668
Male	<5 µg/dL	181 (18.03)	823 (81.97)	1.00			1.00		
	5-10 µg/dL	32 (37.21)	54 (62.79)	2.69	(1.69, 4.29)	<0.001	2.80	(1.74, 4.52)	<0.001
Joint effects of child's sex and lead									
Female	<5 µg/dL	80 (8.06)	912 (91.94)	1.00			1.00		
	5-10 µg/dL	6 (7.89)	70 (92.11)	0.98	(0.41, 2.32)	0.958	0.89	(0.37, 2.15)	0.802
Male	<5 µg/dL	181 (18.03)	823 (81.97)	2.51	(1.90, 3.32)	<0.001	2.54	(1.91, 3.37)	<0.001
	5-10 µg/dL	32 (37.21)	54 (62.79)	6.76	(4.12, 11.06)	<0.001	7.10	(4.29, 11.75)	<0.001

Note: No ADHD was defined as without any ADHD diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

Table 8

online. The joint association of child's sex and early childhood lead levels (age 2 years) with the risk of ADHD diagnosis.

Sex	Lead Level	ADHD, n (%)	NT, n (%)	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Female		81 (11.1)	648 (88.89)	1.00			1.00		
Male		203 (29.90)	476 (70.10)	3.41	(2.57, 4.53)	<0.001	3.51	(2.62, 4.70)	<0.001
Test for sex-based lead (binary) interaction									
Lead effects within child's sex									
Female	<5 µg/dL	78 (11.61)	594 (88.39)	1.00			1.00		
	5-10 µg/dL	3 (5.26)	54 (94.74)	0.42	(0.13, 1.39)	0.155	0.34	(0.10, 1.16)	0.085
Male	<5 µg/dL	173 (27.86)	448 (72.14)	1.00			1.00		
	5-10 µg/dL	30 (51.72)	28 (48.28)	2.77	(1.61, 4.78)	<0.001	3.02	(1.70, 5.34)	<0.001
Joint effects of child's sex and lead									
Female	<5 µg/dL	78 (11.61)	594 (88.39)	1.00			1.00		
	5-10 µg/dL	3 (5.26)	54 (94.74)	0.42	(0.13, 1.39)	0.155	0.35	(0.10, 1.18)	0.091
Male	<5 µg/dL	173 (27.86)	448 (72.14)	2.94	(2.19, 3.95)	<0.001	2.95	(2.18, 3.99)	<0.001
	5-10 µg/dL	30 (51.72)	28 (48.28)	8.16	(4.63, 14.38)	<0.001	8.88	(4.92, 16.03)	<0.001

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

online. The joint association of child's sex and early childhood lead levels with the risk of ADHD diagnosis (further adjusted for maternal lead levels immediately after delivery).

Table 9

Sex	Lead Level	ADHD, n (%)	NT, n (%)	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Female		22 (11.06)	177 (88.94)	1.00			1.00		
Male		60 (31.91)	128 (68.09)	3.77	(2.20, 6.46)	0.000	3.66	(2.07, 6.46)	0.000
Test for sex-based lead (binary) interaction									
Lead effects within child's sex									
Female	<5 µg/dL	21 (11.35)	164 (88.65)	1.00			1.00		
	5-10 µg/dL	1 (7.14)	13 (92.86)	0.60	(0.07, 4.83)	0.632	0.53	(0.06, 5.02)	0.578
Male	<5 µg/dL	54 (31.40)	118 (68.60)	1.00			1.00		
	5-10 µg/dL	6 (37.50)	10 (62.50)	1.31	(0.45, 3.79)	0.617	1.58	(0.50, 5.03)	0.436
Joint effects of child's sex and lead									
Female	<5 µg/dL	21 (11.35)	164 (88.65)	1.00			1.00		
	5-10 µg/dL	1 (7.14)	13 (92.86)	0.60	(0.07, 4.83)	0.632	0.54	(0.06, 5.01)	0.586
Male	<5 µg/dL	54 (31.40)	118 (68.60)	3.57	(2.05, 6.24)	0.000	3.42	(1.91, 6.15)	0.000
	5-10 µg/dL	6 (37.50)	10 (62.50)	4.69	(1.55, 14.21)	0.006	5.14	(1.57, 16.84)	0.007

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal lead levels right after delivery, maternal lead levels, maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

online. The joint association among child's sex, maternal HDL level, maternal stress during pregnancy, and early childhood lead levels with the risk of ADHD diagnosis.

Table 10

Sex	Lead Level	HDL or Stress level	ADHD, n (%)	NT, n (%)	Across sex group			Within sex group		
					Adjusted OR	95% CI	P-Value A	Adjusted OR	.95% CI	P-Value
Joint effects of child's sex, lead, and maternal HDL										
Female	<5 µg/dL	median	30 (12.88)	203 (87.12)	1.06	(0.62, 1.82)	0.833	1.06	(0.61, 1.85)	0.827
	<5 µg/dL	> median	33 (11.46)	255 (88.54)	1.00			1.00		
	5-10 µg/dL	median	2 (8.00)	23 (92.00)	0.62	(0.14, 2.84)	0.539	0.52	(0.11, 2.49)	0.414
Male	5-10 µg/dL	> median	3 (11.54)	23 (88.46)	0.80	(0.22, 2.97)	0.739	0.79	(0.20, 3.04)	0.730
	<5 µg/dL	median	91 (33.96)	177 (66.04)	3.55	(2.25, 5.59)	<0.001	1.45	(0.96, 2.19)	0.075
	<5 µg/dL	> median	56 (25.00)	168 (75.00)	2.49	(1.53, 4.03)	<0.001	1.00		
	5-10 µg/dL	median	17 (56.67)	13 (43.33)	10.03	(4.38, 22.97)	<0.001	4.02	(1.79, 8.99)	0.001
Joint effects of child's sex, lead, and maternal stress										
Female	<5 µg/dL	Not stressful	21 (7.50)	259 (92.50)	1.00			1.00		
	<5 µg/dL	Stressful	59 (14.05)	361 (85.95)	2.00	(1.17, 3.41)	0.011	1.89	(1.09, 3.28)	0.023
	5-10 µg/dL	Not stressful	0 (0.00)	19 (100.00)	NA			NA		
Male	5-10 µg/dL	Stressful	6 (13.33)	39 (86.67)	1.68	(0.62, 4.57)	0.310	1.59	(0.57, 4.42)	0.374
	<5 µg/dL	Not stressful	59 (24.48)	182 (75.52)	4.18	(2.43, 7.20)	<0.001	1.00		
	<5 µg/dL	Stressful	121 (30.17)	280 (69.83)	5.10	(3.08, 8.44)	<0.001	1.21	(0.83, 1.77)	0.312
	5-10 µg/dL	Not stressful	7 (31.82)	15 (68.18)	6.10	(2.18, 17.08)	0.001	1.53	(0.58, 4.05)	0.389
5-10 µg/dL	Stressful	23 (53.49)	20 (46.51)	14.94	(6.88, 32.41)	<0.001	3.53	(1.75, 7.14)	<0.001	

Note: NT was defined as without any neurodevelopmental disorder diagnosis; ADHD was defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birthweight.

Table 11

online. Joint effects of gestational age and early childhood lead levels on the risk of ADHD diagnosis.

Gestational age (<37 weeks)	Lead Level	ADHD, No. (%)	NT, No. (%)	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Term		202 (17.47)	954 (82.53)	1.00			1.00		
Preterm		97 (30.03)	226 (69.97)	2.03	(1.53, 2.69)	<0.001	1.94	(1.43, 2.63)	<0.001
Test for gestational age lead (binary) interaction									
Lead's effects within gestational age group									
Term	<5 µg/dL	177 (16.73)	881 (83.27)	1.00			1.00		
	5-10 µg/dL	25 (25.51)	73 (74.49)	1.70	(1.05, 2.76)	0.030	1.75	(1.06, 2.89)	0.030
Preterm	<5 µg/dL	84 (28.97)	206 (71.03)	1.00			1.00		
	5-10 µg/dL	13 (39.39)	20 (60.61)	1.59	(0.76, 3.35)	0.219	1.63	(0.71, 3.71)	0.246
Joint effects of gestational age and lead									
Term	<5 µg/dL	177 (16.73)	881 (83.27)	1.00			1.00		
	5-10 µg/dL	25 (25.51)	73 (74.49)	1.70	(1.05, 2.76)	0.030	1.76	(1.06, 2.91)	0.028
Preterm	<5 µg/dL	84 (28.97)	206 (71.03)	2.03	(1.50, 2.74)	<0.001	2.61	(1.80, 3.78)	<0.001
	5-10 µg/dL	13 (39.39)	20 (60.61)	3.24	(1.58, 6.62)	0.001	3.76	(1.69, 8.36)	0.001

Note: NT is defined as without any mental disorder diagnosis; ADHD is defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, and mode of delivery.

Table 12

online. Joint effects of birthweight and early childhood lead levels on the risk of ADHD diagnosis.

Birthweight t (<2500g)	Lead Level	ADHD, No. (%)	NT, No. (%)	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
Normal		201 (17.27)	963 (82.73)	1.00			1.00		
Low		98 (31.11)	217 (68.89)	2.16	(1.63, 2.87)	<0.001	2.10	(1.54, 2.85)	<0.001
Test for birthweight lead (binary) interaction									
Lead's effects within birthweight group									
Normal	<5 µg/dL	174 (16.38)	888 (83.62)	1.00			1.00		
	5-10 µg/dL	27 (26.47)	75 (73.53)	1.84	(1.15, 2.94)	0.011	1.89	(1.16, 3.09)	0.011
Low	<5 µg/dL	87 (30.42)	199 (69.58)	1.00			1.00		
	5-10 µg/dL	11 (37.93)	18 (62.07)	1.40	(0.63, 3.08)	0.407	1.22	(0.51, 2.90)	0.658
Joint effects of birthweight and lead									
Normal	<5 µg/dL	174 (16.38)	888 (83.62)	1.00			1.00		
	5-10 µg/dL	27 (26.47)	75 (73.53)	1.84	(1.15, 2.94)	0.011	1.88	(1.15, 3.07)	0.012
Low	<5 µg/dL	87 (30.42)	199 (69.58)	2.23	(1.65, 3.01)	<0.001	2.69	(1.86, 3.90)	<0.001
	5-10 µg/dL	11 (37.93)	18 (62.07)	3.12	(1.45, 6.72)	0.004	3.16	(1.37, 7.26)	0.007

Note: NT is defined as without any mental disorder diagnosis; ADHD is defined as any ADHD diagnosis; the multiple logistic regression model was adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, and mode of delivery.